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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/602,812	06/23/2000	Camellia W. Adams	P1467R2	9612

7590 10/22/2002

Genentech Inc
Attn Wendy Lee
1 DNA Way
San Francisco, CA 94080-4990

EXAMINER
HOLLERAN, ANNE L

ART UNIT	PAPER NUMBER
1642	18

DATE MAILED: 10/22/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/602,812	ADAMS ET AL.	
	Examin r	Art Unit	
	Anne Holleran	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 August 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,4-9,12,13,16-29,34 and 60-62* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) *62* is/are allowed.

6)☒ Claim(s) *1,2,4-6, 8, 9,12,13,16-29,34,60 and 61* is/are rejected.

7)☒ Claim(s) *7* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. The amendment filed August 1, 2002 is acknowledged.

Claims 3, 10, 11, 14, 15, 30-33, 35-59 were canceled.

Claims 60-62 were added.

Claims 1, 2, 4-9, 12, 13, 16-29, 34 and 60-62 are pending and examined on the merits.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Information Disclosure Statement

3. Copies of signed Information Disclosure Statements (PTO-1449) filed April 12, 2001, July 22, 2002 and July 26, 2002 are included with this Office action.

Rejections Withdrawn:

4. The rejection of claims 1-8, 12-13, 16-21, and 24-27 under 35 U.S.C. 112, first paragraph, is withdrawn in light of the amendment.

5. The rejection of 3 and 6-17 under 35 U.S.C. 112, first paragraph, is withdrawn in view of the declaration filed under 37 C.F.R. 1.132.

6. The rejection of claims 1-7, 12-13, 16-18, 20-21, and 24-26 under 35 U.S.C. 103(a) as being anticipated by Greene et al., US Patent 5,842,311, published October 20, 1998 (IDS # 8),

or Arakawa et al., US Patent 5,783,186, published July 21, 1998 (IDS #6), or Hudziak et al., US Patent 5,725,856, published March 10, 1998, as evidenced by Jardines et al., Pathobiology, Vol. 61, pages 268-282, 1993, or Earp et al., Breast Cancer Research and Treatment, Vol. 35, pages 115-132, 1995 (IDS #38), and Grim et al., Am. J. Respir. Cell Mol. Biol., Vol. 15, pages 348-354, September 1996, or Kern et al., Am. J. Respir. Cell Mol. Biol., Vol. 9, pages 448-454, 1993, and Baselga et al., Oncology, Suppl. 2, March 1997 (Baselga I), or Baselga et al., Journal of Clinical Oncology, Vol. 14, No. 3, pages 737-744, March 1996 (Baselga II), in view of Fendly et al., Cancer Research, Vol. 50, pages 1550-1558, March 1, 1990 (IDS #39), or Shepard et al., Journal of Clinical Immunology, Vol. 11, No. 9, pages 117-126, 1991 (IDS #93) is withdrawn upon further consideration and in light of the amendment.

7. The rejection of claims 1-2, 4-6, 12-13, 18, 20-21, and 24-26 under 35 U.S.C. 103(a) as being unpatentable over Grim et al., Am. J. Respir. Cell Mol. Biol., Vol. 15, pages 348-354, September 1996, or Kern et al., Am. J. Respir. Cell Mol. Biol., Vol. 9, pages 448-454, 1993, as evidenced by Jardines et al., Pathobiology, Vol. 61, pages 268-282, 1993, or Earp et al., Breast Cancer Research and Treatment, Vol. 35, pages 115-132, 1995 (IDS #38), in view of Baselga et al., Oncology, Suppl. 2, March 1997, pages 43-48 (Baselga I), or Baselga et al., Journal of Clinical Oncology, Vol. 14, No. 3, pages 737-744, March 1996 (Baselga II) (IDS #24) is withdrawn upon further consideration.

8. The rejection of claims 1-2, 4-6, 12-13, 18, and 20-21 under 35 U.S.C. 103(a) as being unpatentable over Arakawa et al., US Patent 5,783,186, published July 21, 1998 (IDS #6), or

Hudziak et al., US Patent 5,725,856, published March 10, 1998, as evidenced by Jardines et al., Pathobiology, Vol. 61, pages 268-282, 1993, or Earp et al., Breast Cancer Research and Treatment, Vol. 35, pages 115-132, 1995 (IDS #38), in view of Grim et al., Am. J. Respir. Cell Mol. Biol., Vol. 15, pages 348-354, September 1996, or Kern et al., Am. J. Respir. Cell Mol. Biol., Vol. 9, pages 448-454, 1993 is withdrawn upon further consideration.

Rejections Maintained:

9. Prior to setting forth the following art rejections, it is noted that the claims are interpreted to encompass cancers which express EGFR and concurrently overexpress ErbB2. It is known in the art that EGFR (ErbB1) and ErbB2 are often co-expressed in cancer, and further often interact with each other in a common tyrosine kinase activation pathway. See Jardines et al., Pathobiology, Vol. 61, pages 268-282, 1993, page 278, column 2, which determines that many ErbB2 positive patients also overexpress EGFR. Further, Earp et al. teaches that EGFR is overexpressed in "virtually every epithelial malignancy". Additionally it is noted that HER2 and EGFR can interact in an EGF/TGF-alpha dependent manner. (see page 121).

10. The rejection of claims 1-2, 4-6, 12, and 20 under 35 U.S.C. 102(e) as being anticipated by Greene et al., US Patent 5,824,311, published October 20, 1998 (IDS # 8), as evidenced by Jardines et al., Pathobiology, Vol. 61, pages 268-282, 1993, or Earp et al., Breast Cancer Research and Treatment, Vol. 35, pages 115-132, 1995 (IDS # 38) is made and maintained, and applied to claims 8, 9, 16, 27-29 and 61.

Applicants argue that the rejection of claims 1, 2, 4-6, 12 and 20 over Greene is moot because of the amendment to claim 1, incorporating the limitations of canceled claim 3, which was not originally rejected. Upon further consideration, it appears that the limitations of claim 3 do not render the claimed inventions free of the art.

The new limitation added to the claimed inventions is that the antibody blocks the binding of monoclonal antibody to 2C4. Broadly interpreted this limitation may include a wide scope of antibodies that do not necessarily bind to the same epitope as does 2C4, because the ability to block the binding of monoclonal antibody 2C4 may be accomplished by steric hindrance or by a change in the conformation of ErbB2 upon binding of an antibody that causes the epitope for 2C4 to become inaccessible. Therefore, the limitation that antibody blocks the binding of 2C4 to Erbb2 is so broad that many antibodies may be included. Absent evidence to the contrary the antibodies of Greene will block the binding of monoclonal antibody 2C4.

Greene et al., US Patent 5,824,311 teaches a method of treating a patient, which includes humans, by administering a therapeutically effective amount of an antibody which binds ErbB2 and blocks ligand activation of an ErbB receptor. Specifically, Greene teaches that the p185 oncogene (which is the same as ErbB2) has been found active in lung adenocarcinoma, and further provides a method of using monoclonal antibodies which bind to ErbB2 to treat mammalian cancer tumors which express a translation of the neu oncogene on their surfaces (see column 3, line 50-column 5). The antibody of Greene et al. is not conjugated to a cytotoxic compound.

While Greene et al. does not explicitly recite that the cancer which is treated expresses or overexpresses EGFR, or overexpresses an ErbB ligand, including TGF-alpha, numerous cancers

which express ErbB2 inherently co-express, or concurrently overexpress EGFR, and/or the ErbB ligand TGF-alpha. See Jardines et al., Pathobiology, Vol. 61, pages 268-282, 1993, page 278, column 2, which determines that many ErbB2 positive patients also overexpress EGFR and that the ErbB ligand TGF-alpha is expressed at higher levels in malignancies. Further, Earp et al. teaches that EGFR is overexpressed in "virtually every epithelial malignancy", and that TGF-alpha and other EFG family members are overexpressed in cancer. Additionally it is noted that HER2 and EGFR can interact in an EGF/TGF-alpha dependent manner. (see page 121).

The limitation that the antibody has a biological characteristic of 2C4 is considered to be very broad and to include the characteristic of blocking the binding of 2C4 antibody to ErbB2.

11. The rejection of claims 1-2, 4-6, and 20 under 35 U.S.C. 102(e) as being anticipated by Arakawa et al., US Patent 5,783,186 (IDS #6), published July 21, 1998, or Hudziak et al., US Patent 5,725,856, published March 10, 1998, as evidenced by Jardines et al., Pathobiology, Vol. 61, pages 268-282, 1993, or Earp et al., Breast Cancer Research and Treatment, Vol. 35, pages 115-132, 1995 (IDS #38) is made and maintained, and applied to claims 8, 9, 16, 27-29 and 61.

Applicants argue that the rejection of claims 1, 2, 4-6, and 20 over Arakawa or Hudziak is moot because of the amendment to claim 1, incorporating the limitations of canceled claim 3, which was not originally rejected. Upon further consideration, it appears that the limitations of claim 3 do not render the claimed inventions free of the art.

The new limitation added to the claimed inventions is that the antibody blocks the binding of monoclonal antibody to 2C4. Broadly interpreted this limitation may include a wide scope of antibodies that do not necessarily bind to the same epitope as does 2C4, because the

ability to block the binding of monoclonal antibody 2C4 may be accomplished by steric hindrance or by a change in the conformation of ErbB2 upon binding of an antibody that causes the epitope for 2C4 to become inaccessible. Therefore, the limitation that antibody blocks the binding of 2C4 to Erbb2 is so broad that many antibodies may be included. Absent evidence to the contrary the antibodies of either Arakawa or Hudziak will block the binding of monoclonal antibody 2C4.

Arakawa et al., US Patent 5,783,186 teaches a method of treating a patient, which includes humans, by administering by administering a therapeutically effective amount of an antibody which binds ErbB2 and blocks activation of an ErbB receptor. Specifically, Arakawa teaches that the HER2 oncogene (which is the same as ErbB2) has been found active in numerous cancers, including breast, ovarian, gastric, prostate, and colorectal, and further provides a method of using monoclonal antibodies which bind to ErbB2 to treat mammalian cancer tumors which express ErbB2 on their surfaces (see column 6, lines 12-17, and lines 53-59). The antibody of Arakawa et al. is not conjugated to a cytotoxic compound.

Hudziak et al., US Patent 5,725,856 teaches a method of treating a patient, which includes humans, by administering a therapeutically effective amount of an antibody which binds ErbB2 and blocks activation of an ErbB receptor. Specifically, Hudziak teaches that the HER2 oncogene (which is the same as ErbB2) has been found active in numerous cancers, including breast, renal, gastric and salivary cancers, and further provides a method of using monoclonal antibodies which bind to ErbB2 to treat mammalian cancer tumors which express ErbB2 on their surfaces (see column 4, lines 27-31, column 6, lines 31-35, column 7, lines 50-56, column 8, lines 27-30, column 10, lines 46-53, column 11, lines 32-40). The antibody of Hudziak et al. is

not conjugated to a cytotoxic compound. Hudziak et al. also teaches that EGFR and TGF-alpha are associated with an increased proliferative effect in a carcinoma cell line (column 3, lines 28-65)

While Arakawa et al. and Hudziak et al. do not explicitly recite that the cancer which is treated expresses or overexpresses EGFR, or overexpresses an ErbB ligand, including TGF-alpha, numerous cancers which express ErbB2 inherently co-express, or concurrently overexpress EGFR, and/or the ErbB ligand TGF-alpha. See Jardines et al., page 278, which determines that many ErbB2 positive patients also overexpress EGFR and that the ErbB ligand TGF-alpha is expressed at higher levels in malignancies. Further, Earp et al. teaches that EGFR is overexpressed in "virtually every epithelial malignancy", and that TGF-alpha and other EFG family members are overexpressed in cancer. Additionally it is noted that HER2 and EGFR can interact in an EGF/TGF-alpha dependent manner. (see page 121).

The limitation that the antibody has a biological characteristic of 2C4 is considered to be very broad and to include the characteristic of blocking the binding of 2C4 antibody to ErbB2.

New Grounds of Rejection:

12. Claims 1, 2, 4-6, 8, 9,, 12, 13, 16, 18-21, 24-29, and 61are rejected under 35 U.S.C. 103(a) as being unpatentable over Greene et al., US Patent 5,842,311, published October 20, 1998 (IDS #8), or Arakawa et al., US Patent 5,783,186, published July 21, 1998 (IDS #6), or Hudziak et al., US Patent 5,725,856, published March 10, 1998, as evidenced by Jardines et al., Pathobiology, Vol. 61, pages 268-282, 1993, or Earp et al., Breast Cancer Research and

Treatment, Vol. 35, pages 115-132, 1995 (IDS #38), in view of Grim et al., Am. J. Respir. Cell Mol. Biol., Vol. 15, pages 348-354, September 1996).

Greene, Hudziak , or Arakawa fail to teach that the anti-ErbB2 antibody can be used to treat lung cancer and non-small cell lung cancer. However, Grim et al. teaches a method of treating lung cancer by administering an antibody fragment which binds to ErbB2 (see abstract, and especially pages 350 and 353), thus teaching that the ErbB2 receptor is a therapeutic target in lung cancer and that antibody fragments may be used for treatment purposes. Therefore it would be *prima facie* obvious to one of ordinary skill in the art at the time of applicant's invention to treat human lung cancer patients with an ErbB2 antibody, and it would have been prima facie obvious to one of ordinary skill in the art to use fragments of the antibodies of Greene, Hudziak or Arakawa in methods of treatment.

Greene, Hudziak or Arakawa fail to teach treatment regimens. However, the ability to establish treatment regimens is well known to those of ordinary skill in the art. Thus, it would have been prima facie obvious to one of ordinary skill in the art to have modified the methods of either Greene, Hudziak, or Arakawa to include treatment regimens.

13. Claims 7 and 60 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The basis for this rejection is that the disclosure of monoclonal antibody 2C4 is not representative of the genus of antibodies that block TGF-alpha

activation of MAPK. Thus, the specification lacks adequate written description of the methods using this genus of antibodies.

The disclosure is limited to the description of monoclonal antibody 2C4. The disclosure fails to demonstrate that applicant was in possession of other antibodies that blocked TGF-alpha activation of MAPK. Thus, applicants do not appear to be in possession of the genus of antibodies that are recited in the claimed methods.

Conclusion

Claim 62 is allowed. Claim 17 is free of the art, but is objected to for depending from a rejected claim.

Any inquiry concerning this communication or earlier communications from the Office should be directed to Anne Holleran, Ph.D. whose telephone number is (703) 308-8892. Examiner Holleran can normally be reached Monday through Friday, 9:30 am to 2:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, Ph.D. can be reached at (703) 308-3995.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist at telephone number (703) 308-0196.

Anne L. Holleran
Patent Examiner
October 21, 2002

ANTHONY C. CAPUTA
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600